

ASN DIALYSIS ADVISORY GROUP

ASN DIALYSIS CURRICULUM

Management of Traditional Cardiovascular Risk Factors in ESRD (Hypertension, Dyslipidemia, Glycemic Control)

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Management of Traditional Cardiovascular Risk Factors (Hypertension)

- **Individualize BP targets and agents according to age, co-existent CV disease, co-morbidities, and tolerance of treatment. (Not Graded)**
- **BP goal < 140/90 mmHg with diet, lifestyle modification and hemo/peritoneal dialysis**
- **RAAS blocker may confer survival benefit**
- **Observational data with few randomized controlled trials**

Management of Traditional Cardiovascular Risk Factors (Dyslipidemia)

- **Measure total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) Follow-up measurement of lipid levels is not required**
- **Statins or statin/ezetimibe combination not be initiated. (2A)**
- **In patients already receiving statins or statin/ezetimibe combination at the time of dialysis initiation, suggest that these agents be continued. (2C)**
- **3 large randomized controlled drug trials with statins no clear benefit**

Management of Traditional Cardiovascular Risk Factors (Glycemia)

- **Target A1C ~ 7%, and above 7.0% (53mmol/mol) in individuals with comorbidities or limited life expectancy and risk of hypoglycemia. (2C)**
- **Glycemic control should be part of a multifactorial intervention**
- **Oral and injectable agents effective in type 2 DM (avoid sulfonylureas)**
- **Insulin dose should be reduced by ½ in most**
- **No randomized controlled trials in this population**

Hypertension and Outcomes in Dialysis Populations

Relationship between BP and CV mortality is complex and controversial

Owing to BP measurement technique and timing

Some studies indicate low BP is associated with increased mortality

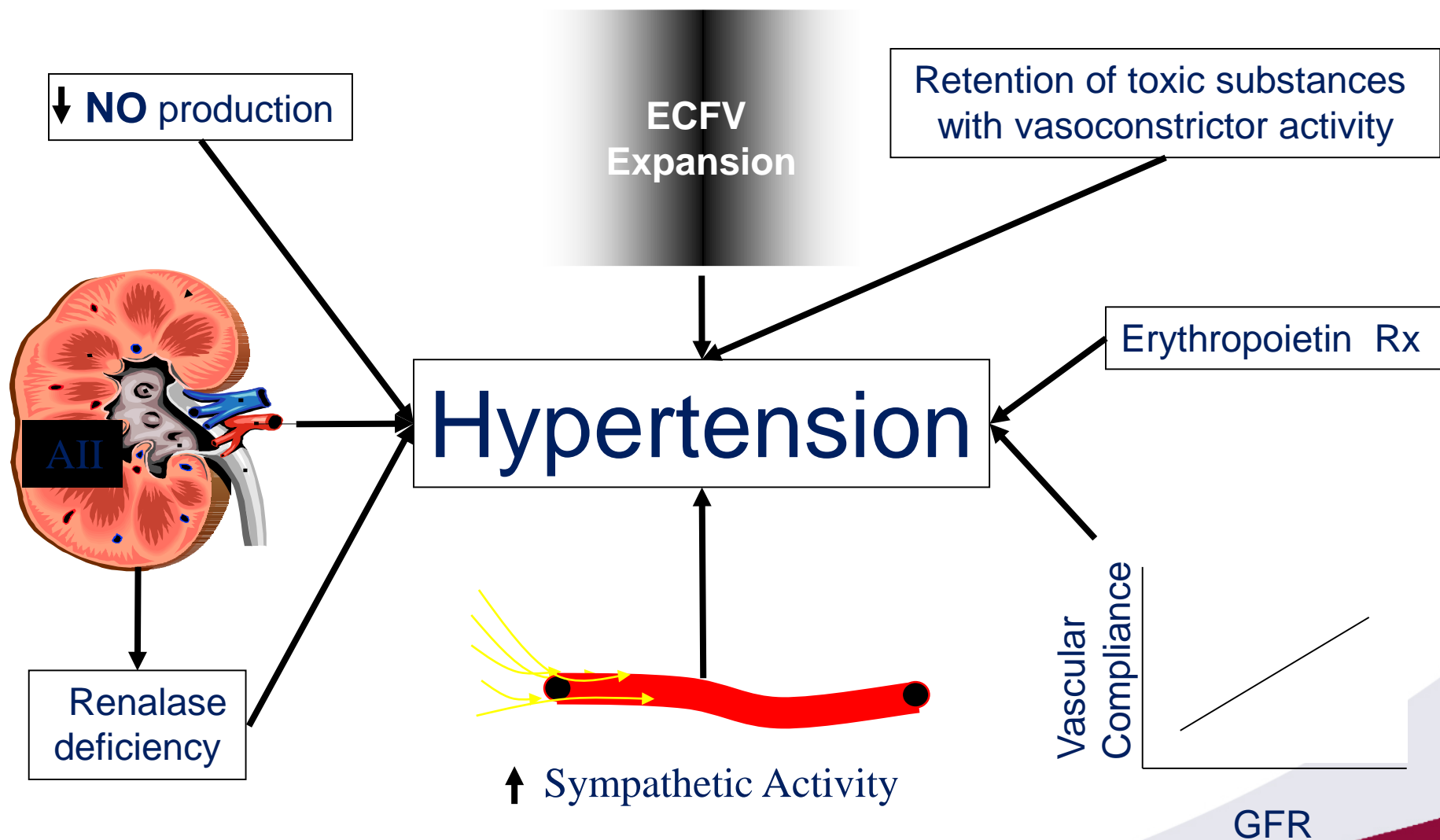
Observational data indicate that dialysis populations are at higher risk of

- **Heart failure**
- **Coronary artery disease**
- **Left ventricular hypertrophy**

Higher stroke mortality

Predicts CV events in those with known cardiovascular disease

Pathogenesis of Hypertension in Dialysis



Hypertension Management in Dialysis 1

Predialysis and postdialysis BP goals should be <140/90 mm Hg and <130/80 mm Hg, respectively. (C)

Management of hypertension in hemodialysis and peritoneal dialysis patients requires:

- **attention to fluid status and dry weight (iterative trial and error)**
- **adjustment of antihypertensive medications. (B)**

Excessive fluid accumulation (B):

- **Education and regular counseling by dietitians**
- **Low sodium intake (2–3 g/day sodium intake)**
- **Increased ultrafiltration, longer dialysis**
- **More than 3 hemodialysis treatments per week,**
- **Additional exchanges for peritoneal dialysis**

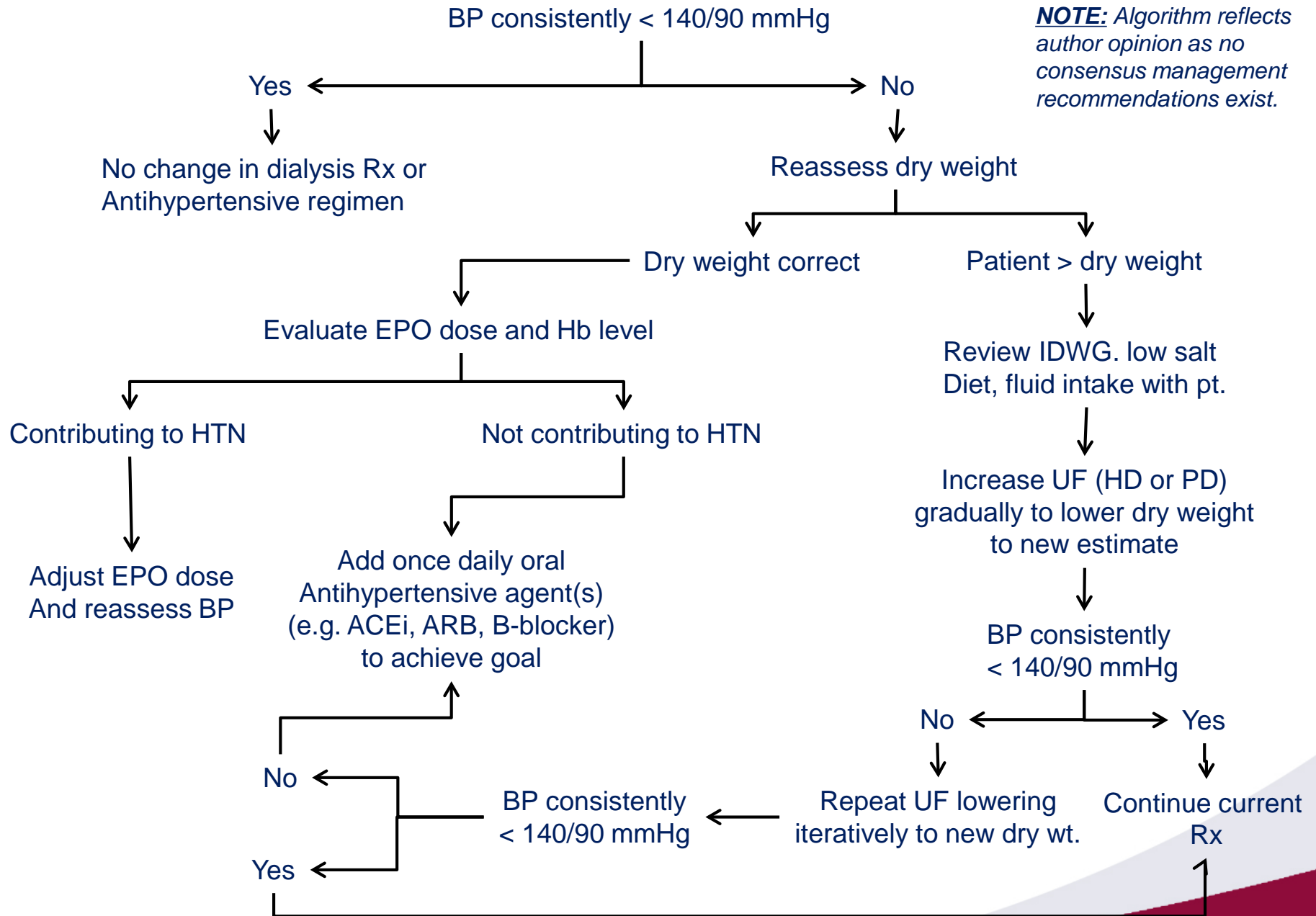
Hypertension Management in Dialysis 2

- 12.4a Drugs that inhibit the renin-angiotensin system, such as ACE inhibitors or angiotensin II-receptor blockers should be preferred because they cause greater regression of LVH, reduce sympathetic nerve activity, reduce pulse wave velocity, may improve endothelial function, and may reduce oxidative stress. (C)**

- 12.4b Antihypertensive drugs should be given preferentially at night, because it may reduce the nocturnal surge of blood pressure and minimize intradialytic hypotension, which may occur when drugs are taken the morning before a dialysis session. (C)**

- 12.4c In patients with difficult-to-control hypertension, the dialyzability of antihypertensive medications should be considered**

Management Algorithm for Hypertension Control in ESRD



Specific therapy 1

Strategy

Prolong dialysis time

Add time to dialysis by one of the following a) additional conventional treatment; b) nocturnal dialysis; c) daily dialysis; d) additional exchanges for peritoneal dialysis

Rationale

More effective and safe volume removal

Reduces risk for intradialytic hypotension

Restore Kt/V

Specific therapy 2

Strategy

Treat with antihypertensives:

- Consider ACEi or ARB
- If necessary add-on “selective” beta-blocker, calcium channel blocker, clonidine patch (avoid α -blocker in DM)

Rationale:

- Some clinical trials suggest better outcome
- Add-on medication to get to goal

Specific therapy 3

Strategy

For hemodialysis: lower dialysate temperature and increase dialysate calcium

Rationale

Reduce risk for intradialytic hypotension

Dyslipidemia

KDIGO

Clinical Trials

Recommendations

2013 KDIGO Recommendations for Dyslipidemia Management in Adults with Stage 5 CKD*

1.1: Evaluation with a lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) recommended. (1C)

1.2: Follow-up measurement of lipid levels is not required for the majority of patients. (Not Graded)

2.3.1: Suggest that statins or statin/ezetimibe combination not be initiated. (2A)

2.3.2: In patients already receiving statins or statin/ezetimibe combination at the time of dialysis initiation, suggest that these agents be continued. (2C)

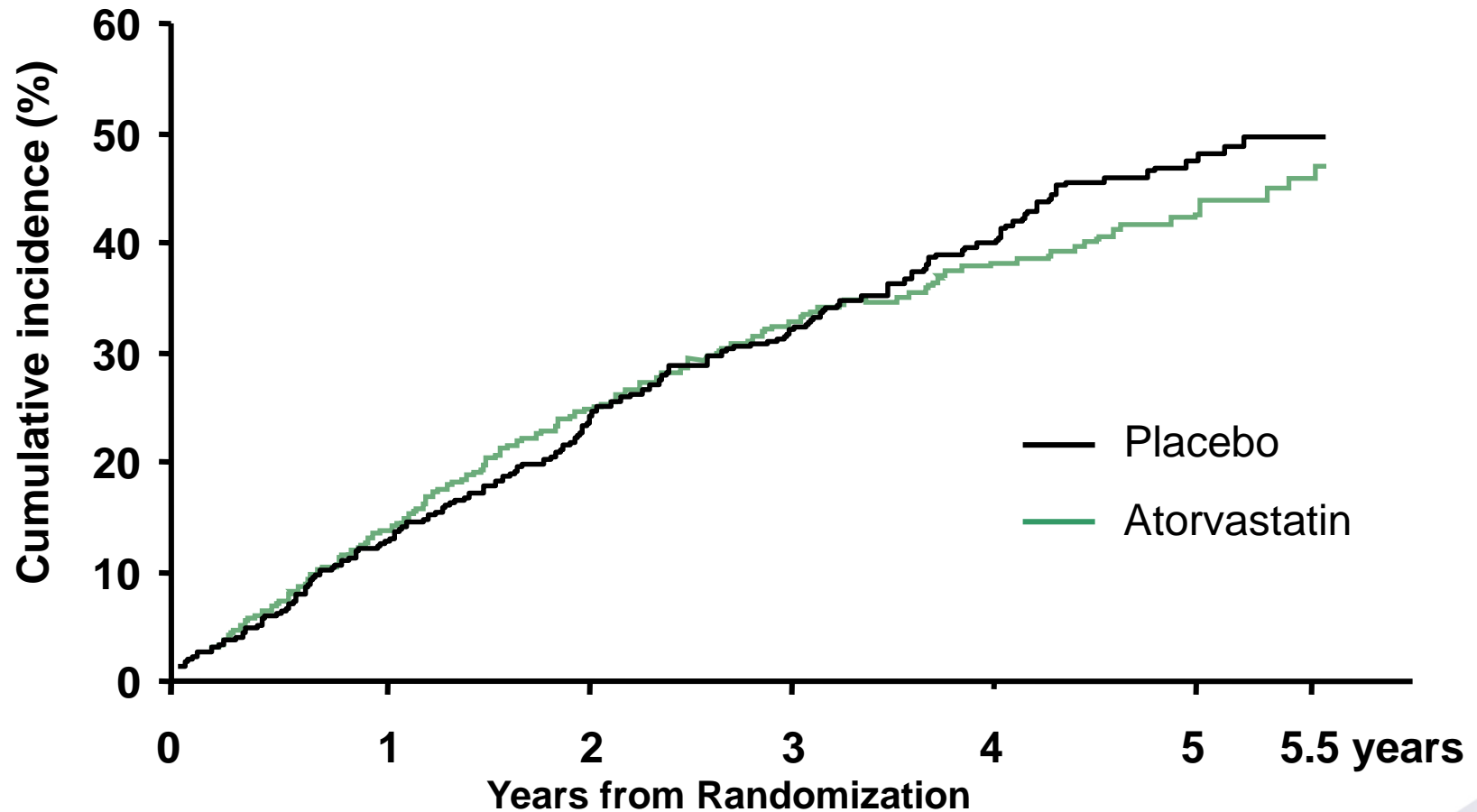
2.4: In adult kidney transplant recipients, we suggest treatment with a statin. (2B)

*Capital letter in parenthesis indicates level of evidence



Primary composite end point

Relative Risk Reduction 8 % (95 % CI: 0.77-1.10, P=0.37)



Placebo	636	532	383	252	136	51	29
Atorvastatin	619	515	378	252	136	58	19

Median follow-up time of 4 years

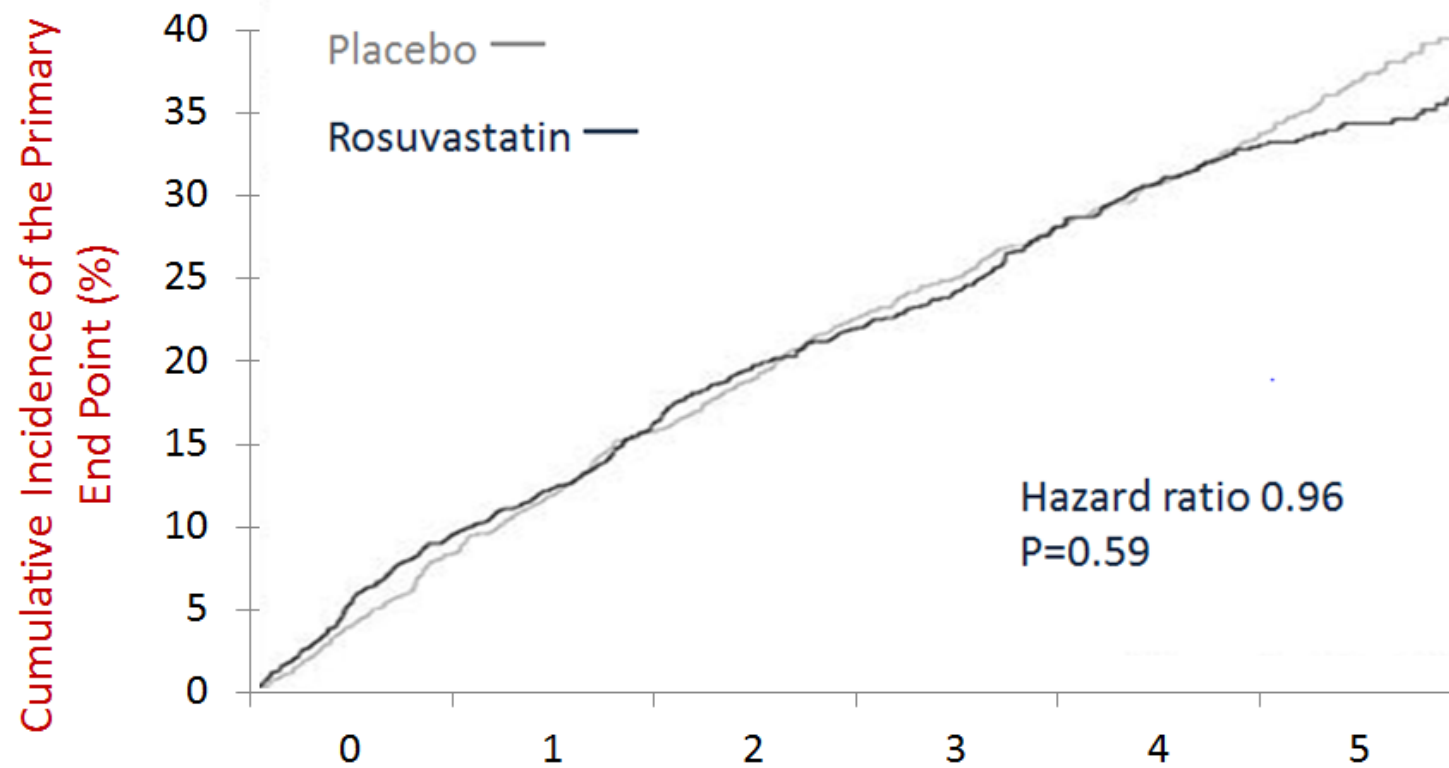
Adapted from Wanner et al. N Engl. J. Med. 353;3 www.nejm.org July 21, 2005

4D Conclusions

- In patients with type 2 diabetes mellitus undergoing hemodialysis, the initiation of treatment with atorvastatin 10 mg daily lowered the LDL cholesterol level.....
- but had no significant effect on the composite primary end point of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke



AURORA: Primary Composite Endpoint



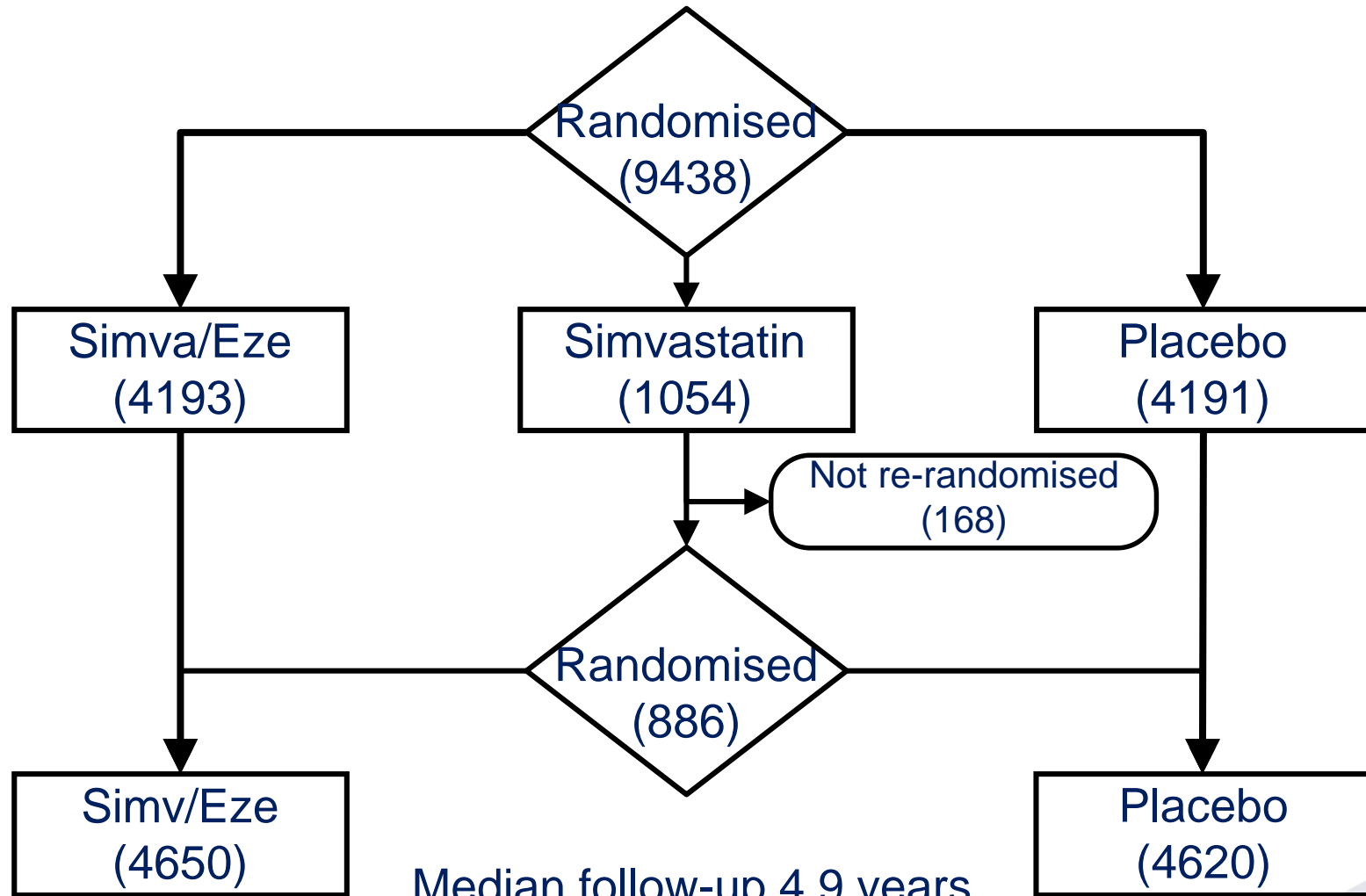
Not at Risk

Placebo	1384	1163	952	809	534	153
Rosuvastatin	1390	1152	962	826	551	148

Conclusions

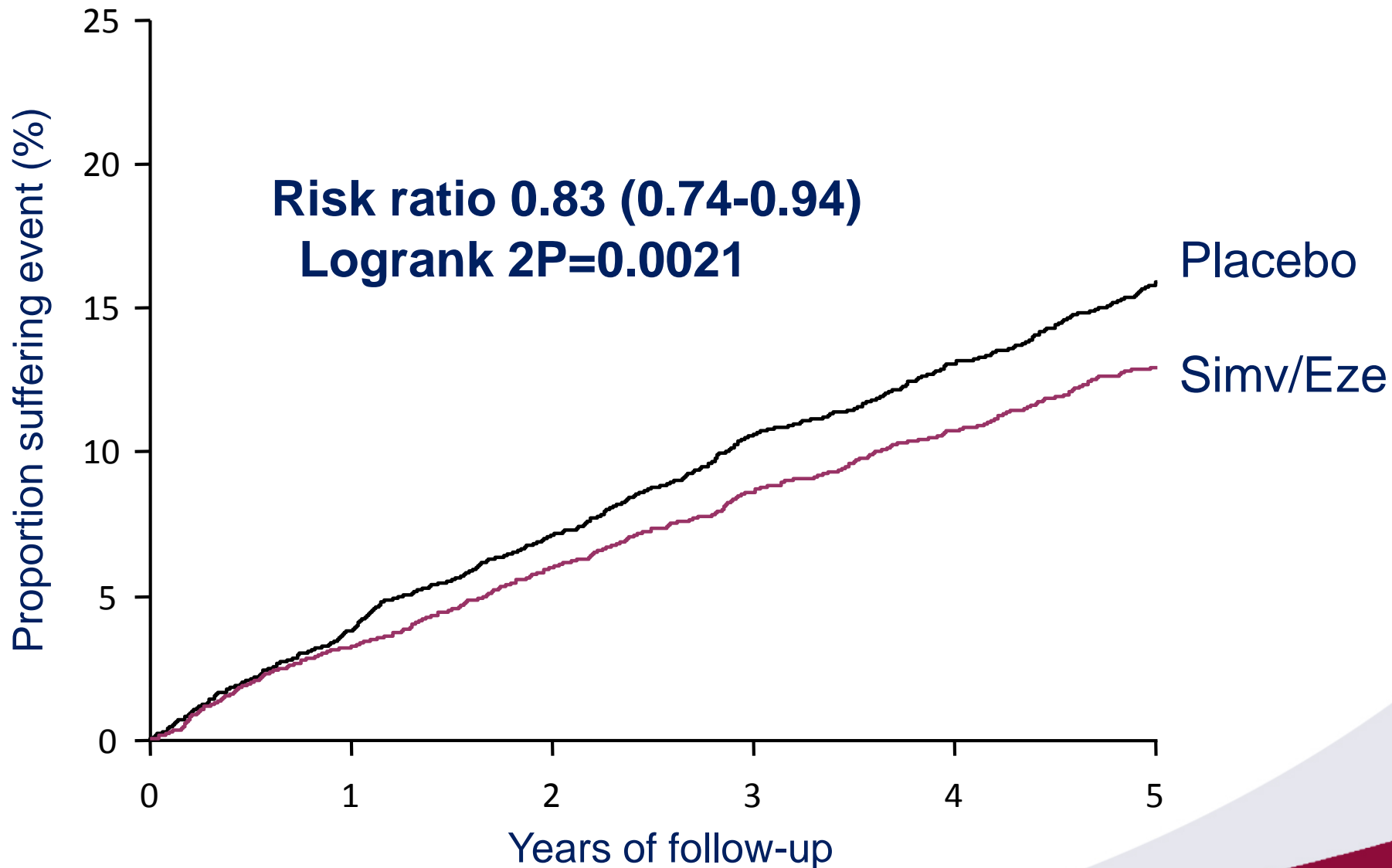
- In patients undergoing hemodialysis, the initiation of treatment with rosuvastatin lowered the LDL cholesterol level.....
- but had no significant effect on the composite primary end point of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke

SHARP: Randomization structure



Median follow-up 4.9 years
Lost to mortality follow-up 1.5%

SHARP: Major Atherosclerotic Events in Patients with CKD including Dialysis



SHARP: Conclusion

Reduction of LDL cholesterol with simvastatin 20 mg plus ezetimibe 10 mg daily safely reduced the incidence of major atherosclerotic events in a wide range of patients with advanced chronic kidney disease.

KDIGO Research Recommendation

“An extended observational study should be undertaken of the SHARP study cohort to determine whether the reduction in major atherosclerotic events resulting from 5 years of LDL-C lowering persists in the long-term, and whether LDL-C lowering significantly delays renal disease progression in people with non-dialysis-dependent CKD and eGFR ≥ 60 ml/min/1.73m²”

Rationale for Glycemic Control in ESRD

Prevent acute and subacute metabolic complications of uncontrolled glycemia

Advanced glycation product elevation associated with mortality risk

However, A1C may not be reflective of glucose control in people with CKD (reduced red cell life span), interpret with caution. Blood glucose daily logs may be more reliable

Elevated cardiovascular risk

No controlled trials demonstrating improved outcomes with any particular A1c or other marker

KDIGO Guideline for Glycemic Control

- Target A1c of ~ 7.0% (53 mmol/mol) to prevent or delay progression of the microvascular complications of diabetes, including diabetic kidney disease. (1A)
- 3.1.16: Not treating to an HbA1c target of < 7.0% (< 53 mmol/mol) in patients at risk of hypoglycemia. (1B)
- 3.1.17: Target A1c should be extended above 7.0% (53mmol/mol) in individuals with comorbidities or limited life expectancy and risk of hypoglycemia. (2C)
- 3.1.18: Glycemic control should be part of a multifactorial intervention strategy addressing blood pressure control and cardiovascular risk, promoting the use of angiotensin-converting enzyme inhibition or angiotensin receptor blockade, statins, and antiplatelet therapy where clinically indicated. (Not Graded)

Management of Glycemic in ESRD

Pharmacologic management is complicated by several factors:

- altered insulin resistance and glucose metabolism
- altered pharmacokinetics and safety profile of antihyperglycemic agents,
- concerns about the effect of drugs on kidney function,
- altered nutritional status
- higher risk of hypoglycemia.

Poor Outcomes at High A1c in hemodialysis patients: Observational Data

Post-Hoc analysis of the 4 D study during median of 4 years follow up

- graded relationship between inferior glycemic control and mortality due to sudden cardiac death

Patients with HbA1c levels $> 8.0\%$ had a more than 2-fold higher risk of sudden death compared with those with HbA1c levels $\leq 6.0\%$ (HR, 2.14).

Furthermore, with each 1% increase in HbA1c level, the risk of sudden death, after statistical adjustments, increased by 18%.

Drug Rx for Glycemia in ESRD I

Pharmacotherapy should be individualized.

Target A1c value 6-7%, a fasting blood glucose < 140 mg/dL, and a postprandial glucose < 200 mg/dl

Oral antidiabetic drugs; glipizide, sitagliptin, and saxagliptin may be used in ESRD.

- Glipizide, starting with 2.5 mg daily, should be reserved for ESRD patients with a hemoglobin A1c value less than 8.5%.

Thiazolidinediones may cause fluid overload and thus should be avoided in ESRD.

Dosing Adjustments by CKD Stage for Drugs Used to Treat Hyperglycemia

Class	Drug	Dosing Recommendation CKD Stages 3, 4, or Kidney Transplant	Dosing Recommendation Dialysis
First-generation sulfonylureas	Acetohexamide	Avoid	Avoid
	Chlorpropamide	Reduce dose by 50% when GFR <70 and ≥ 50 mL/min/1.73 m ² Avoid when GFR <50 mL/min/1.73 m ²	Avoid
	Tolazamide	Avoid	Avoid
	Tolbutamide	Avoid	Avoid
Second-generation sulfonylureas	Glipizide	Preferred sulfonylurea No dose adjustment necessary	Preferred sulfonylurea No dose adjustment necessary
	Gliclazide	Preferred sulfonylurea No dose adjustment necessary Not available in US	Preferred sulfonylurea No dose adjustment necessary Not available in US
	Glyburide	Avoid	Avoid
	Glimepiride	Initiate at low dose, 1 mg daily	Avoid
Alpha-glucosidase inhibitors	Acarbose	Not recommended in patients with SCr >2 mg/dL	Avoid
	Miglitol	Not recommended in patients with SCr >2 mg/dL	Avoid
Biguanides	Metformin	Contraindicated with kidney dysfunction defined as SCr ≥ 1.5 mg/dL in men or ≥ 1.4 mg/dL in women	Avoid
Meglitinides	Repaglinide	No dose adjustment necessary	No dose adjustment necessary
	Nateglinide	Initiate at low dose, 60 mg before each meal	Avoid
Thiazolidinediones	Pioglitazone	No dose adjustment necessary	No dose adjustment necessary
	Rosiglitazone	No dose adjustment necessary	No dose adjustment necessary
Incretin mimetic	Exenatide	No dose adjustment necessary	No dose adjustment necessary
Amylin analog	Pramlintide	No dose adjustment necessary for GFR 20-50 mL/min/1.73 m ²	No data available
DPP-4 inhibitor	Sitagliptin	Reduce dose by 50% (50mg/day) when GFR < 50 and ≥ 30 mL/min/1.73 m ² and by 75% (25 mg/day) when GFR < 30 mL/min/1.73 m ²	Reduce dose by 75% (25 mg/day)

Drug Rx for Glycemia in ESRD II

In most, insulin dose should be decreased by ~ 50% from amount prior to ESRD (i.e. GFR > 10 ml/min).

Long-acting insulin (e.g. glargine [Lantus]) or NPH insulin for basal requirements, along with a rapid-acting insulin analogue (e.g. lispro) before meals two or three times daily.

Newer insulins such as glargine and lispro are more favorable than NPH and regular insulin, but are costly

- type 1 diabetes, insulin should be started at 0.5 IU/kg, ~ half the calculated dose in patients without renal failure.
- type 2 diabetes, insulin Rx should be started at a total daily dose of 0.25 IU/kg.
- further adjustments based on self-monitored BG

Glucagon-like peptide1 (GLP-1) receptor agonists associated with nausea and vomiting in patients and may not be well tolerated.

Alpha-glucosidase inhibitors, bile acid sequestrants, dopamine 2 agonists, and amylin mimetics, are of limited use in patients with CKD.

Management of Glycemia in ESRD: Summary

Glycemic control and monitoring are complex.

In PD patients:

- require close attention owing to glucose absorption.

- home BG monitoring may be very important here.

Patients especially susceptible to hypoglycemia, so diabetic drug Rx requires special caution.

Ongoing diabetes education, with an emphasis on how to recognize and treat hypoglycemia.

Consider consulting an endocrinologist with expertise in managing diabetes in ESRD

Effects of glycemic control in patients with ESRD have not yet been studied in a randomized clinical trial.